Systematic review of HER2 breast cancer testing
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CRD summary
This review aimed to compare immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) testing for determining HER2 status in breast cancer; FISH was assumed to be the reference standard. Data were sparse and studies were poorly reported. The conclusion that IHC testing was insufficient to select patients for therapy was supported by the data and is likely to be reliable.

Authors' objectives
To assess the analytical validity and clinical utility of HER2 testing using immunohistochemistry (IHC) or fluorescence in situ hybridisation (FISH) to determine which breast cancer patients were suitable for trastuzumab therapy.

Searching
MEDLINE, EMBASE, CRD databases, The Cochrane Library and European Agency for the Evaluation of Medical Products (EMEA), Food and Drug Administration (FDA) and INAHTA databases were searched to September 2006. The search strategy was reported in full and included some methodological terms for diagnostic accuracy studies. Bibliographies of identified systematic reviews were screened for additional articles. Studies published in any language were included.

Study selection
Studies of any design that compared at least FISH and IHC for HER2 status testing in breast cancer patients were eligible for inclusion. Included studies were required to report the following outcomes: sensitivity, specificity, concordance, detection limit, validity, reliability and reproducibility. Most articles evaluated the Hercep Test (IHC) and the PathVysion test (FISH). Testing was carried out using a variety of different antibodies.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The methodological quality of included studies was assessed using a checklist based on the Spanish Critical Appraisal Skills Programme (CASPe) scale. The checklist assessed: clear statement of objective; randomisation; adequate accounting for drop-outs; blinding of study personnel; similarity of groups at baseline and treatment of groups during the trial; precision, accuracy and generalisability of results; and whether clinically important outcomes were assessed.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
FISH was assumed to be the reference standard and data were extracted to assess concordance between IHC score category and FISH result. Concordance was calculated as FISH positivity in each IHC score category (number of FISH positive participants in the IHC score category/total number of participants in the IHC score category). IHC score categories were 0, 1+, 2+ and 3+ (0 and 1+ were considered negative, 2+ indeterminate and 3+ strongly positive).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined in a narrative synthesis.

Results of the review
Seventeen studies were included in the review. Twelve (number of participants unclear) provided data on concordance between IHC score and FISH result and only data for these 12 studies were reported; six studies provided data for all IHC score categories. Blinded interpretation of results was reported for only two studies. Standardisation of test procedures and reporting of results were generally poor. In four studies FISH was carried out only in cases of indeterminate (IHC 2+) results.
The proportion of FISH positive results in IHC negative cases ranged from 0 to 20% for IHC 0 cases (eight studies) and from 3.13 to 51.27% for IHC 1+ cases (eight studies). For IHC positive cases (3+), the proportion of FISH positives ranged from 50% to 96% (11 studies). For IHC indeterminate cases (2+), the proportion of FISH positives ranged from 8.3% to 92.3% (10 studies).

Using data from the six studies that reported FISH positive rates for all IHC scores, median FISH positive rates were 3.5% for IHC 0, 5.8% for IHC 1+, 17% for IHC 2+ and 83.5% for IHC 3+.

**Authors' conclusions**

IHC testing was not sufficient for appropriate selection of patients who were suitable for trastuzumab therapy; FISH was a more accurate and reliable test.

**CRD commentary**

This review aimed to compare diagnostic strategies for determining HER2 status in breast cancer (HER2 status can be used to select patients for certain treatment options). Appropriate inclusion criteria were defined and a range of sources were searched for relevant studies without language restriction. However, the search strategy included methodological terms for diagnostic accuracy, an approach which was likely to reduce the sensitivity of the search and may have resulted in loss of relevant studies. Measures were taken to avoid error/bias in study selection; it was unclear whether similar measures were applied to the rest of the review process. The methodological quality of included studies was assessed, but the tool used was one designed for randomised controlled trials (studies included in this review were all observational studies of diagnostic performance). However, the authors highlighted quality issues of relevance to this review. Given the apparent between-study heterogeneity and poor quality of available data, use of a narrative synthesis was appropriate. The authors’ conclusion that IHC testing was not sufficient to select patients for trastuzumab therapy was supported by data presented and is likely to be reliable. However, the statement that IHC was a suitable method for obviously negative cases (0 and 1+) and FISH was a more accurate, reliable and precise test for confirming or excluding HER2 status in indeterminate (2+) and positive (3+) cases was not supported by the data; from the studies that reported the proportion of FISH positives in all IHC categories, up to 50% of IHC 1+ cases were FISH positive. As FISH was assumed to be the reference standard and, therefore, 100% accurate, the review could not provide data that evaluated the accuracy of FISH.

**Implications of the review for practice and research**

**Practice:** The authors stated that IHC was a suitable method for obviously negative cases (0 and 1+) and FISH was a more accurate, reliable and precise test for confirming or excluding HER2 status in indeterminate (2+) and positive (3+) cases.

**Research:** The authors made no recommendations for research.

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